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Beta-Blockers in Syncope: The Jury Is Still Out

Madrid et al. (1) are to be commended for assessing the efficacy of beta-blockers in neurocardiogenic syncope. Syncope is a common problem, and beta-blockers are commonly used to attempt to treat this disorder despite a paucity of randomized data.

Unfortunately, design limitations preclude this study from providing definitive answers as to the role of beta-blocking drugs in neurocardiogenic syncope. Previous papers have identified predictors of beta-blocker success, including the presence of tachycardia during the tilt table test, the need for isoproterenol to induce syncope, and an acute response to beta-blockers (2,3). By including a high percentage of tilt-negative patients (60%), the investigators may have inadvertently diluted a potential treatment effect. The researchers' own data in their Figure 2 suggest a differential response to study medication based upon the result of the tilt table test. We agree with Madrid et al. (1) that tilt tests are not an ideal diagnostic modality, but a better tool is not presently available. We are now validating objective criteria quantitatively for the causes of syncope that make use of a structured history to diagnose neurocardiogenic syncope (1). Without such a tool, a positive tilt test remains the diagnostic standard.

In the accompanying editorial to the Madrid et al. (1) article, Dr. Sra (5) correctly points out that the assessment of therapy in neurocardiogenic syncope is difficult. A single recurrence of syncope is not an ideal end point due to symptom clusters and long symptom-free periods. This problem is not unique to syncope research; it is also seen in other disorders such as paroxysmal atrial fibrillation. We have previously reported that the time to first syncope recurrence after a positive tilt table test correlates very well with the frequency of syncope after a positive tilt table test (6). Time to first syncope recurrence is an appropriate end point for such studies, but it can be supplemented with other end points such as syncope burden and presyncope burden.

We agree with Dr. Sra (5) about the need for a large-scale multicenter trial to answer the question of beta-blockers for neurocardiogenic syncope. We are presently conducting a multinational, double-blind, placebo-controlled study of oral metoprolol in patients with at least three lifetime episodes of neurocardiogenic syncope and a positive head-up tilt table test. In the study, which is funded by the Canadian Institutes of Health Research, we are enrolling 220 patients, each of whom will be on blinded therapy for one year. The primary end point is time to first syncope recurrence, and secondary end points include the burden of syncope and presyncope, and the quality of life over the full year.

Madrid et al. (1) may eventually be found to be correct in concluding that atenolol specifically and beta-blockers in general are not effective in decreasing or delaying symptoms in patients with neurocardiogenic syncope. However, the final answer is not yet known.

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REPLY

We appreciate the interest of Sheldon et al. in our article and the opportunity to respond to his letter. We are aware of his concerns regarding the methodology of our study, considering the diagnosis of vasovagal syncope based on the typical clinical history. We do not question the great clinical value of the tilt test, but in this technified medicine we also need to consider the value of simple things such as the anamnesis and physical examination. We recognize the progress in the knowledge of physiology, which the tilt test has rendered, but nevertheless it is not the gold standard for the diagnosis of vasovagal syncope, with its limited sensitivity and specificity and its dependence on the protocol.

In our study, only those patients with a clear anamnesis of vasovagal syncope were included. In fact, more than 700 patients with unexplained syncope were evaluated, and in the end only 50 patients were eligible for the study, including those patients with clear clinical history of vasovagal syncope who were highly symptomatic. A complete study to discard other possible causes of syncope was carried out in all patients. Moreover, there was no new etiological diagnosis of syncope during the follow-up (1). We want to emphasize that despite the lack of efficacy of atenolol, the

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median number of syncopal events dropped in both groups during the follow-up (from 3 to 2 and 0), simply after evaluating them, performing the tilt table test and explaining the pathogenesis of the disease. This fact may explain Dr. Sra's (2) skepticism on the medical capacity to prove the benefit of any treatment for vasovagal syncope. This could also be the reason why almost any treatment that has been tested for the therapy of vasovagal syncope has been considered to be effective (3). But we do not know whether a clinical diagnosis, reassuring the patient and explaining to the patient the postural maneuvers can be enough to provide symptomatic relief in most patients.

We would like to congratulate Sheldon et al. for his efforts in establishing the role of beta-blockers for the treatment of vasovagal syncope. We share his frustrations in the treatment of this disabling and frequent disease. There is no doubt that new randomized and controlled studies are needed to reach a definitive answer. We are happy to have raised doubts on the efficacy of the drugs most commonly used for this pathology.

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Heterogeneity of Response to Lipid-Lowering Therapy

I read with great interest the article by Penny et al. (1) on changes in endothelium-dependent vasomotor responses in mildly diseased coronary arteries after lipid-lowering therapy. In that report, the investigators studied angiographic responses to acetylcholine (Ach) along successive 3-mm coronary segments. On average there was a small improvement in vasoresponsiveness to Ach after lipid-lowering therapy. Changes in responsiveness correlated with a marker of oxidized low-density lipoprotein (LDL), but not with LDL or total cholesterol levels. As the title implies, the researchers concluded that, overall, lipid-lowering drug treatment reverses coronary endothelial dysfunction.

Although the reported observations generally support the broad concept that, on average, lipid lowering in hypercholesterolemic individuals with atherosclerotic disease can improve endothelial function, they also appear to suggest a potentially important additional and perhaps counterintuitive hypothesis: that the coronary vasomotor responses of some patients may actually react adversely to lipid-lowering therapy. Reiterating the original observations of El-Tamimi et al. (2), who showed adjacent segments in the same artery can show vasodilatory and vasoconstrictive responses, the investigators document an extraordinary heterogeneity in responses of individual coronary segments to Ach, both at baseline and after treatment. More remarkable, the changes in intraindividual coronary artery segment responses after therapy appear to occur in both directions, with a large number of segments showing a decline in vasodilation or vasoconstriction at follow-up. Though the majority of the "most constricted" segments at baseline demonstrated improved responses at follow-up, only 4 of the 29 patients showed arteries that lacked some segmental "deterioration" in function. Judging from Figure 3 in the Penny et al. (1) study, where individual segment response changes were plotted, it appears that 40% to 45% of patients showed a predominantly contrarian response, with more segments showing a decline in vasomotor responsiveness rather than "improvement." Whereas this may represent regression to the mean, the mechanism is unclear. Although the graphical expression of the data suggests moderation of responses at follow-up, it leaves some ambiguity with respect to the severity of the deteriorated segmental responses, and it seems possible that the magnitude of the heterogeneity may have been underestimated by the methods employed.

The benefits of lipid-lowering therapy for reducing clinical events in patients with hypercholesterolemia and coronary artery disease have been well established. The observations by Penny et al. (1), as well as the results of the Coronary Artery Reactivity After Treatment with Simvastatin (CARATS) trial (3), which failed to show significant improvement in endothelium-dependent coronary vasomotor and blood flow responses in patients treated for six months with simvistatin, highlight a degree of complexity and inter- and intraindividual variability of response to statin and/or lipid-lowering therapy that is currently poorly understood, and yet is one that raises important questions. Are these heterogeneous responses the result of random variability, or do the data imply that there is a subgroup of patients whose coronaries may respond poorly or even adversely to lipid-lowering therapy? Because the investigators have demonstrated a correlation between changes in responsiveness and levels of circulating oxidized LDL (which are not reliably reduced by statin therapy [4]), do the results imply that oxidized LDL levels may help identify those patients who are unlikely to show improvement in endothelial function with lipid-lowering therapy alone, and may need more aggressive additional treatment? Would the clinical benefit of statin therapy be greater if we could select likely patient/coronary "responders" from "nonresponders" or worse, "adverse responders"? Given that multiple mechanisms may be involved in the benefit of statin therapy, this interpretation might be overly simplistic. Nevertheless, the observations of Penny et al. (1) suggest variability in coronary responses to lipid-lowering therapy that may be clinically relevant and warrant further investigation.

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